ABSTRACT

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Title of diploma thesis: *In vitro* transport of abacavir across the monolayer of Caco-2 cells; interaction with etravirine and rilpivirine.

Abacavir belongs among nucleoside reverse transciptase inhibitors (NRTIs) representing a basic component of combined antiretroviral therapy used in treatment of HIV-positive patients [1]. Etravirine and rilpivirine are newer non-nucleoside reverse transcriptase inhibitors (NNRTIs) combined in cART together with NRTI.

ATP-dependent transporters, so called ABC transporters, are able to affect pharmacokinetic properties of drugs, thus they are important site of drug-drug interactions affecting absorption, distribution and excretion level. P-glycoprotein (Pgp, ABCB1) and BCRP (ABCG2) belong among the most clinically important ABC transporters able to cause drug-drug interactions.

The aim of this thesis was to introduce and optimize the method for evaluation of drug absorption using monolayers of Caco-2 human intestine cell lines, whose integrity was verified by evaluating TEER (transepithelial electrical resistance). This model was also used for abacavir transport studies. Significant asymmetry was observed in transport of abacavir across Caco-2 monolayer in basolateral-apical direction in contrast to apical-basolateral direction. The asymmetry was completely reduced by adding elacridar (dual inhibitor Pgp and BCRP). The follow up transport study with rilpivirine and etravirine revealed that both antiretrovirotics affect abacavir permeability across

the cell monolayer, most probably due to inhibition of ABC eflux tranporters (Pgp and BCRP). Based on our results, we suggest that both, etravirine and rilpivirine, are able to cause drug-drug interactions that might affect abacavir absorption and lead to its increased bioavailability. Such interaction might call for adjustments in abacavir dosage when co-administered with one of those NNRTIs in clinical settings.